CONVERSION OF 2-IODOANILINE INTO (*Z*)-3-METHYLENE-2,3-DIHYDROINDOLE DERIVATIVES

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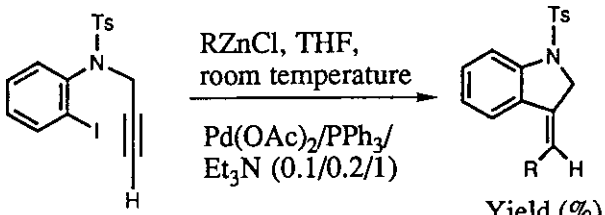
Abstract- Treatment of *N*-(2-iodophenyl)-*N*-2-propynyl-*p*-tolylsulfonamide with various organozinc chlorides in the presence of palladium acetate, triphenylphosphine, and 1 equiv. of triethylamine in tetrahydrofuran gives (*Z*)-3-alkylidene-2,3-dihydroindoles *via* intramolecular Heck-type reaction and successive cross coupling reactions.

The use of intramolecular Heck-type reaction and successive cross coupling reaction in the construction of stereoselective double bond has attracted considerable interest recently.[1-6] We have reported a unique methodology involving palladium catalyzed cyclization and cross coupling to synthesize various kinds of cyclic compounds containing a stereospecific double bond structure at the exocyclic position.[1-3] The stereospecificity of the reaction gives us information on the mechanism of the cyclization and cross coupling in this reaction.[1] We now report that this procedure can be also applied to the synthesis of a variety of (*Z*)-3-alkylidene-2,3-dihydroindoles from *N*-(2-iodophenyl)-*N*-2-propynyl-*p*-tolylsulfonamide (**1**) which is easily obtained by tosylation and propargylation of *o*-iodoaniline. As representative alkyl-, alkenyl-, alkynyl-, phenyl- and heteroaryl-zinc chlorides were chosen in the cross coupling process.

As indicated by the structures of the products (**2** - **9**) as well as the results summarized in Table I, the introduction of substituents such as alkyl

Table I. Reactions of **1** with Organozinc Chlorides in the Presence of Palladium Catalyst



1

R =	Yield (%)
Ph –	2(76)
	3(72)
	4(67)
	5(56)
n-Bu –	6(67)
	7(69)
n-Bu-C≡C–	8(61)
Me_3Si-C≡C–	9(53)

, alkenyl, alkynyl, aryl, and heteroaryl groups in the exocyclic position of (*Z*)-3-alkylidene-2,3-dihydroindoles can now be readily achieved by the palladium catalyzed cyclization and cross coupling reactions.

We have previously found that the use of the catalytic system including palladium acetate (0.1 equiv.), triphenylphosphine (0.25 equiv.), and triethylamine (3 equiv.) in the reaction of 1-iodo-2-(2-propynyloxy)benzene can provide not only in fair to good yields of cyclized and coupled products but also in very low yields of direct coupled products which are

always undesired in our studies.[1,2] We found that the reaction running at room temperature in tetrahydrofuran (THF) in the presence of 1 equiv. of triethylamine, 0.2 equiv. of triphenylphosphine, and 0.1 equiv. of palladium acetate could reach the optimized yields of the cyclized and cross coupled products. The direct coupled products of the above reactions have not been detected from their crude ^{1}H-nmr spectra analysis. The need for palladium catalyst has been established in all cases by running control experiments. The *Z* structure of the exocyclic double bond in the products was deduced from their 2D NOESY spectra analyses. The use of organolithium instead of organozinc chloride in all the reactions gave also the desired products but in very low yields. It has been noted that for compounds containing a β-hydrogen such as *n*-butylzinc chloride the cross coupling is difficult in the palladium catalyzed reactions.[7] However, it can be successfully employed in this intramolecular cyclization and cross coupling reactions.

EXPERIMENTAL SECTION

Melting points are uncorrected. Precoated silica gel 60F-254 on aluminum plates made by EM Chemical Company was used for thin layer chromatography. Purification by column chromatography was carried out with EM Reagents silica gel 60 (70-230 mesh ASTM). High pressure liquid chromatography (hplc) separation was performed at a flow rate of 1.5 ml/min by use of two Chemco Pak 10 x 250 columns packed with Chemcosorb 5-ODS-H. Glc analyses were performed on a 3.2 m x 3.1 mm column packed with SE-30 (5% on chromosorb W). The purity of each compound was judged to be ≥95% by hplc, ^{1}H-nmr, and ^{13}C-nmr spectral analyses. Zinc chloride was dried before using at 100°C at 1 mm for 3 h. THF was distilled from sodium benzophenone ketyl immediately prior to use.

N-(2-Iodophenyl)-*N*-2-propynyl-*p*-tolylsulfonamide (**1**): A solution of tosyl chloride (1.91 g, 10 mmol) in 20 ml of THF was added dropwise at room temperature to a solution of *o*-iodoaniline (2.19 g, 10 mmol) and pyridine

(0.79 g, 10 mmol) in 30 ml of THF. After stirring for another 3 h, 10 ml of water and 50 ml of ether were added to the reaction mixture. The organic layer was washed with water (10 ml x 2) and concentracted to give *N*-(2-iodophenyl)-*p*-tolylsulfonamide (2.73 g, 76%) as a pale yellow solid: mp 87-88°C (lit.,[8] 85°C). ^{1}H-Nmr ($CDCl_3$, TMS) δ 2.36 (s, 3 H), 6.7-6.9 (m, 2 H), 7.1-7.4 (m, 3 H), 7.5-7.7 (m, 4 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 21.55, 92.31, 122.42, 126.80, 127.38, 129.43, 129.58, 135.81, 137.42, 139.04, 144.17 ppm. Ir (KBr) ν 3320 (w), 1210 (m), 1160 (s), 1090 (m), 910 (m), 900 (m), 810 (m), 770 (m), 740 (m), 710 (m), 660 (m), 560 (m) cm^{-1}. Ms *m/z* 373 (M^+), 218, 155, 139. No further purification step for this product is needed in running the following reactions. To a solution of *N*-(2-iodophenyl)-*p*-tolylsulfonamide (1.80 g, 5 mmol) in 10 ml of THF were added pyridine (1.98 g, 25 mmol) and propargyl bromide (0.72 g, 6 mmol) at room temperature. The reaction mixture was then stirred at room temperature for another 4 h. The reaction mixture was quenched by adding 20 ml of water. The organic compounds were then extracted by using ether (15 ml x 3) and concentrated. The product was purified by column chromatography (20% EtOAc in hexane as eluant) to give **1** as a pale yellow solid (1.62 g) in 79 % yield : mp 117-117.5°C. ^{1}H-Nmr ($CDCl_3$, TMS) δ 2.16 (t, *J* = 2 Hz, 1 H), 2.46 (s, 3 H), 4.12 (dd, *J* = 18, 2 Hz, 1 H), 4.77 (dd, *J* = 18, 2 Hz, 1 H), 7.0-7.6 (m, 5 H), 7.73 (d, *J* = 8 Hz, 2 H), 7.93 (dd, *J* = 8, 1 Hz, 1 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 21.51, 40.58, 50.74, 73.95, 102.42, 128.28, 128.65, 129.35, 130.34, 131.23, 136.63, 140.22, 140.64, 143.86 ppm. Ir (KBr) ν 3285 (w), 1460 (m), 1350 (s), 1160 (s), 1095 (m), 850 (m), 715 (m), 660 (m), 570 (m), 550 (w) cm^{-1}. Ms *m/z* 411 (M^+), 284, 256, 220, 155, 139, 129, 102, 91, 83. Hrms calcd for $C_{16}H_{14}NO_2IS$ 410.9790, found: 410.9795.

(*Z*)-2,3-Dihydro-3-(phenylmethylene)-1-tosyl-1*H*-indole (**2**). A Representative Procedure for Palladium Catalyzed Stereoselective Synthesis of (*Z*)-3-Alkylidene-2,3-dihydroindole. To a solution of **1** (1.24 g, 3 mmol) in 5 ml of THF was added a mixture of triethylamine (0.30 g, 3 mmol),

palladium acetate (0.07 g, 0.3 mmol), and triphenylphosphine (0.16 g, 0.6 mmol) in 5 ml of THF at room temperature. After stirring at room temperature for 30 min, phenylzinc chloride solution, prepared by mixing phenylmagnesium bromide (5.9 ml of 1.52 *N* in THF) and zinc chloride (9 ml of 1 *N* in THF) at room temperature, was added to the reaction mixture. The reaction mixture was then stirred for another 2 h and quenched by adding water (30 ml) at 0°C. The organic layer was extracted with ether (20 ml x 3). The combined organic layer was washed with water (20 ml) and brine (20 ml), dried over $MgSO_4$, filtered, concentrated, and purified by column chromatography (silica gel, 10% ether in hexane as eluant) and hplc (methanol) to give **2** (0.82 g, 76%) as a colorless liquid. ^{1}H-Nmr ($CDCl_3$, TMS) δ 2.35 (s, 3 H), 4.64 (d, *J* = 2.6 Hz, 2 H), 6.48 (s, 1 H), 6.72 (t, *J* = 7.4 Hz, 1 H), 7.0-7.4 (m, 9 H), 7.6-7.8 (m, 3 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 21.33, 55.97, 114.87, 121.02, 122.99, 123.94, 127.15, 128.07, 128.21, 128.35, 129.57, 129.81, 132.88, 133.62, 136.34, 144.13, 145.63 ppm. Ir (neat) ν 1595 (m), 1460 (m), 1360 (s), 1165 (s), 1110 (m), 965 (m), 910 (m), 810 (m), 735 (s), 700 (m), 670 (m), 600 (m), 580 (m), 540 (m) cm^{-1}. Ms *m/z* 361 (M^+), 206. Hrms calcd for $C_{22}H_{19}NO_2S$ 361.1137, found 361.1150. *Anal.* Calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.30. Found: C, 72.68; H, 5.35.

(*Z*)-2,3-Dihydro-(2-furanylmethylene)-1-tosyl-1*H*-indole (3). ^{1}H-Nmr ($CDCl_3$, TMS) δ 2.35 (s, 3 H), 4.66 (d, *J* = 2.5 Hz, 2 H), 6.15 (t, *J* = 2.5 Hz, 1 H), 6.34 (d, *J* = 3.3 Hz, 1 H), 6.45 (dd, *J* = 3.3, 1.9 Hz, 1 H), 7.04 (dt, *J* = 8.6, 1.0 Hz, 1 H), 7.1-7.3 (m, 3H), 7.49 (d, *J* = 1.6 Hz, 1 H), 7.6-7.8 (m, 3 H), 8.30 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 21.40, 56.80, 108.03, 109.57, 111.60, 114.54, 123.54, 125.32, 127.17, 127.99, 129.65, 130.11, 130.42, 133.68, 141.92, 142.77, 144.23, 145.99, 151.18 ppm. Ir (neat) ν 1595 (m), 1450 (m), 1360 (s), 1210 (m), 1170 (s), 1110 (m), 1090 (m), 1015 (m), 970 (m), 910 (m), 810 (m), 735 (s), 665 (s), 575 (s), 540 (m) cm^{-1}. Ms *m/z* 351 (M^+), 299, 279, 196. Hrms calcd for $C_{20}H_{17}NO_3S$ 351.0929, found 351.0913. *Anal.* Calcd for $C_{20}H_{17}NO_3S$: C, 68.36; H, 4.88.

Found: C, 68.29; H, 4.81.

(*Z*)-2,3-Dihydro-3-(2-thienylmethylene)-1-tosyl-1*H*-indole (**4**). ^{1}H-Nmr ($CDCl_3$, TMS) δ 2.37 (s, 3 H), 4.64 (d, *J* = 2.6 Hz, 2 H), 6.41 (t, *J* = 2.6 Hz, 1 H), 6.84 (dt, *J* = 8.4, 1 Hz, 1 H), 7.0-7.1 (m, 3 H), 7.2-7.3 (m, 3 H), 7.44 (d, *J* = 7.9 Hz, 1 H), 7.7-7.8 (m, 3 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 21.44, 56.14, 112.95, 114.90, 123.21, 123.65, 124.17, 125.53, 126.59, 127.21, 127.63, 127.92, 129.68, 130.30, 133.67, 134.86, 138.24, 144.27, 145.85 ppm. Ir (neat) ν 1600 (m), 1460 (m), 1360 (s), 1210 (m), 1165 (s), 1110 (m), 1090 (m), 965 (m), 810 (m), 750 (m), 730 (m), 700 (s), 670 (s), 575 (s), 540 (m) cm^{-1}. Ms *m/z* 367 (M^+), 212. Hrms calcd for $C_{20}H_{17}NO_2S_2$ 367.0701, found 367.0719. *Anal.* Calcd for $C_{20}H_{17}NO_2S_2$: C, 65.37; H, 4.66. Found: C, 65.24; H, 4.60.

(*Z*)-2,3-Dihydro-3-(2-pyridinylmethylene)-1-tosyl-1*H*-indole (**5**). ^{1}H-Nmr ($CDCl_3$, TMS) δ 2.35 (s, 3 H), 4.70 (d, *J* = 2.6 Hz, 2 H), 6.45 (t, *J* = 2.6 Hz, 1 H), 6.92 (t, *J* = 7.1 Hz, 1 H), 7.1-7.3 (m, 5 H), 7.6-7.8 (m, 4 H), 8.27 (d, *J* = 7.8 Hz, 1 H), 8.64 (d, *J* = 4.8 Hz, 1 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 21.51, 56.82, 114.61, 120.14, 121.76, 123.28, 124.31, 126.71, 127.27, 127.82, 129.75, 131.01, 133.80, 136.35, 136.54, 144.38, 146.50, 149.09, 155.13 ppm. Ir (neat) ν 1585 (m), 1455 (m), 1350 (s), 1210 (m), 1160 (s), 1090 (m), 970 (m), 750 (m), 680 (m), 660 (m), 570 (m), 540 (m) cm^{-1}. Ms *m/z* 362 (M^+), 298, 207. Hrms calcd for $C_{21}H_{18}N_2O_2S$ 362.1089, found 362.1071. *Anal.* Calcd for $C_{21}H_{18}N_2O_2S$: C, 69.59; H, 5.01. Found: 69.52; H, 4.87.

(*Z*)-2,3-Dihydro-3-(pentylene)-1-tosyl-1*H*-indole (**6**). ^{1}H-Nmr ($CDCl_3$, TMS) δ 0.90 (t, *J* = 7.2 Hz, 3 H), 1.2-1.5 (m, 4 H), 2.2-2.4 (m with one singlet at δ 2.36, 5 H), 4.4-4.5 (m, 2 H), 5.4-5.5 (m, 1 H), 7.00 (dt, *J* = 7.6, 1 Hz, 1 H), 7.1-7.3 (m, 3 H), 7.42 (d, *J* = 7.9 Hz, 1 H), 7.5-7.6 (m, 3 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 13.91, 21.52, 22.40, 28.08, 31.58, 55.80, 114.89, 123.49, 123.73, 124.70, 126.82, 127.30, 128.92, 129.66, 129.87, 130.60, 134.00, 144.07, 145.24 ppm. Ir (neat) ν 1600 (m), 1450 (m), 1360

(s), 1165 (s), 1115 (m), 1090 (m), 970 (m), 810 (m), 750 (m), 660 (m), 575 (m), 540 (m) cm^{-1}. Ms *m/z* 341 (M^+), 279, 259, 241, 149, 129. Hrms calcd for $C_{20}H_{23}NO_2S$ 341.1449, found 341.1444. *Anal.* Calcd for $C_{20}H_{23}NO_2S$: C, 70.35; H, 6.79. Found: C, 70.28; H, 6.71.

(*Z*)-2,3-Dihydro-3-(2-phenyl-2-propenylene)-1-tosyl-1*H*-indole (**7**). ^{1}H-Nmr ($CDCl_3$, TMS) δ 2.40 (s, 3 H), 4.65 (d, *J* = 2.6 Hz, 2 H), 5.33 (s, 1 H), 5.68 (s, 1 H), 6.16 (s, 1 H), 6.78 (t, *J* = 7.4 Hz, 1 H), 7.15 - 7.40 (m, 9 H), 7.50 (d, *J* = 7.9 Hz, 1 H), 7.70 (d, *J* = 8.3 Hz, 2 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 21.47, 56.00, 115.06, 120.85, 123.26, 125.00, 126.16, 127.11, 127.29, 128.01, 128.38, 129.64, 129.82, 133.90, 134.05, 138.66, 143.46, 144.13, 145.70 ppm. Ir (neat) ν 1355 (m), 1205 (m), 1165 (s), 1110 (m), 1090 (m), 740 (m), 725 (m), 700 (m), 655 (m) cm^{-1}. Ms *m/z* 387 (M^+), 279, 232, 217, 167, 149. *Anal.* Calcd for $C_{24}H_{21}NO_2S$: C, 74.39; H, 5.46. Found: C, 74.33; H, 5.40.

(*Z*)-2,3-Dihydro-3-(2-heptynylene)-1-tosyl-1*H*-indole (**8**). ^{1}H-Nmr ($CDCl_3$, TMS) δ 0.95 (t, *J* = 7.6 Hz, 3 H), 1.4-1.7 (m, 4 H), 2.3-2.5 (m with one singlet at δ 2.36, 5 H), 4.57 (d, *J* = 1 Hz, 2 H), 5.49 (t, *J* = 1 Hz, 1 H), 7.02 (t, *J* = 7 Hz, 1 H), 7.2-7.4 (m, 3 H), 7.6-7.8 (m, 3 H), 8.18 (d, J = 8 Hz, 1 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ 13.58, 19.61, 21.54, 22.03, 30.72, 55.31, 79.00, 99.06, 114.49, 123.41, 124.29, 127.15, 129.76, 130.60, 140.82, 144.36 ppm. Ir (neat) ν 1450 (m), 1370 (s), 1170 (s), 1125 (s), 1090 (s), 970 (m), 750 (s), 660 (s), 575 (s), 540 (m) cm^{-1}. Ms *m/z* 365 (M^+), 256, 236. Hrms calcd for $C_{22}H_{23}NO_2S$ 365.1449, found 365.1444. *Anal.* Calcd for $C_{22}H_{23}NO_2S$: C, 72.30; H, 6.34. Found: 72.18; H, 6.26.

(*Z*)-2,3-Dihydro-3-(3-trimethylsilyl-2-propynylene)-1-tosyl-1*H*-indole (**9**). ^{1}H-Nmr ($CDCl_3$, TMS) δ 0.21 (s, 9 H), 2.36 (s, 3 H), 4.58 (d, *J* = 2.7 Hz, 2 H), 5.51 (t, *J* = 2.7 Hz, 1 H), 7.04 (t, *J* = 8.2 Hz, 1 H), 7.22 (d, *J* = 8.1 Hz, 2 H), 7.33 (dt, *J* = 8.5, 1.0 Hz, 1 H), 7.67 (d, *J* = 6.6 Hz, 2 H), 7.76 (d, *J* = 8.2 Hz, 1 H), 8.26 (d, *J* = 7.7 Hz, 1 H) ppm. ^{13}C-Nmr ($CDCl_3$, TMS) δ -0.32, 21.40, 55.28, 97.96, 102.26, 103.29, 114.50, 123.32, 124.79,

127.05, 128.69, 129.71, 131.14, 133.53, 143.69, 144.38, 145.74 ppm. Ir (neat) ν 2120 (m), 1590 (m), 1460 (s), 1360 (s), 1250 (s), 1210 (s), 1160 (s), 1115 (m), 1090 (s), 1060 (s), 840 (s), 750 (s), 660 (s), 580 (s), 540 (m) cm^{-1}. Ms *m/z* 381 (M^+), 226. Hrms calcd for $C_{21}H_{23}NO_2SSi$ 381.1219, found 381.1222. *Anal.* Calcd for $C_{21}H_{23}NO_2SSi$: C, 66.10; H, 6.08. Found: C, 66.02, H, 6.14.

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